UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Review of PMN 91-391- Twenty-Eight Day Oral Toxicity Test in Rats

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The following is a review of a 28 day oral toxicity study in rats on PMN 91-391. [redacted]

[redacted]

PMN 91-391 Identification

Chemical Identification: Reported as an acrylic acid ester reacted with 3-(2-hydroxyethyl)2-oxazolidone. No structure available.

Physical state: Liquid

Use: "Reactive diluent in UV or electron beam curing of lithographics in industrial varnishes".

Conclusion:

Four groups of Sprague-Dawley rats, six per sex per dose, were administered PMN 91-391 daily by gavage for 28 days. The doses were 0, 40, 125 or 400 mg/kg per day. The PMN produced extensive inflammation and/or necrosis and/or hyperkeratosis and/or ulceration and/or hyperplasia of the forestomach in all the male and female rats at the high dose level. Only one rat was examined from the low dose group and found to have edema of the mucosa. No animals were histologically examined at the mid dose level or in controls. On this basis, the report states that a no-effect level for PMN 91-391 was not achieved. This reviewer is in agreement with the submitter that there is a no no-effect level under the conditions of this study.

Since PMN 91-391 is an acrylate ester which will break down to acrylic acid, the toxicity findings in the forestomach of rats with PMN 91-391 concur with those of the NTP report No. 259 on ethyl acrylate. Ethyl acrylate also metabolizes to acrylic acid.

In addition, the PMN 91-391 produced microgranulomas in the liver of male and female rats. The incidence was 92% at the high dose and 50% in controls. The statistical significance according to the Fisher Exact method produces a P=0.034 and is statistically significant. There are a large number of reasons for the formation of granulomas observed in the livers in this experiment. Granulomata (inflammatory) may be formed due to the presence of bacteria, fungi or viruses. Other factors may produce granulomata such as foreign bodies. Unless the etiology is clear, the statistical significance of granulomas observed in this experiment may not be pertinent to the toxicological profile of the PMN.

Basis for the conclusion:

After a period of acclimatization, six Sprague-Dawley rats per sex per dose were administered PMN 91-391 by gavage, at 0, 40, 125 and 400 mg/kg per day for 28 days. The protocol followed for testing was, according to the submitter, that of the O.E.C.D. and also according to The Directive of the Official Journal of the European Economic Community (84/449/E.E.C., 19th September 1984).

Clinical signs were recorded once per day and mortality was checked twice per day. Food consumption and body weight were recorded weekly. Hematology, blood biochemical examinations and urinalysis were completed at week four. At the end of the study, all the surviving animals were sacrificed, a necropsy was done and histopathology was completed on some of the organs.

There were no mortalities during the test period. The only clinical sign seen was hypersalivation in 2 of six males treated at 125 mg/kg and in 6/6 males and 5/6 females beginning after six or seven days of treatment at 400 mg/kg. Slight retardation of body weight gain was observed in males at the 125 and 400 mg/kg dose levels. Food consumption in the treated rats was similar to the control groups. There were no changes attributable to the administration of test material in regards to hematology, blood chemistry, or urinalysis. Organ weights showed no differences between control or treated groups.

In the histological examination, microgranulomas in the liver were found in 11 of 12 rats (both sexes) or 92% at the high dose level. Control animals had liver microgranulomas in 6 of 12 male and female rats or 50%. None of the animals in the intervening dose levels were examined microscopically for granulomas. The exact nature of the granuloma and the etiology of the granuloma have not been clarified. The incidence of granuloma in both sexes (twelve animals) at 400 mg/kg is statistically significant with P=.034 using the Fisher's Exact test.

In regards to lesions of the forestomach, at the high dose of 400 mg/kg, the PMN produced extensive lesions in a majority of the animals. The report states there were "ulcerations and/or an inflammatory reaction of the serosa and/or a fibrino-leucocytic exudate and/or a fibrinoid necrosis of the submucosa and/or the presence of granulation tissue of the submucosa and/or the presence of inflammatory cells in the submucosa and/or hyperkeratosis and epithelial hyperplasia." However, none of the forestomach of male or female rats were histologically examined in the control group. Only one rat was examined histologically at the low dose and was found to have edema of the stomach mucosa. According to the O.E.C.D. Guidelines, "Histological examination should be performed on the preserved organs or tissues of the high dose group and the control group. These

examinations may be extended to animals of other dosage groups." On the basis of exercising due caution, this reviewer is in agreement with the submitter that the No Observable Effect Level (NOEL) could not be determined under the conditions of this study.